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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/645,321	08/25/2000	SATOSHI KOIZUMI	5.1183	3262

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EXAMINER

RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 06/24/2002

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/645,321

Applicant(s)

KOIZUMI ET AL.

Examiner

Manjunath N Rao

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 April 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 6-18 is/are rejected.
- 7) ☒ Claim(s) 4-5 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18 are still at issue and are present for examination.

Applicants' arguments filed on 4-11-02, paper No. 7, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3, 6-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vann(a) et al. (Glycobiology, 1997, Vol. 7(5):697-701), or Vann(b) et al. (J. Biol. Chem., 1987, Vol. 262(36):17556-62) and Maru et al. (Carbohydrate Research Vol. 306:575-578). Claims 1-3, 6-18 are drawn to a process of producing N-acetylneuraminic acid (NANA) which comprises allowing a culture of a microorganism having NANA aldolase activity or NANA synthetase activity or a treated matter of the culture, a culture of a microorganism capable of producing pyruvic acid or a treated matter culture when a microorganism having NANA aldolase activity is used in the step above, or culture of a microorganism capable of producing phosphoenol pyruvic acid or a treated matter of the culture when a microorganism having NANA-synthetase activity is used in the first above step, N-acetyl mannosamine and an energy source which is

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necessary for the formation of pyruvic acid or PEP to be present in an aqueous medium to form and accumulate NANA in the aqueous medium and recovering NANA from the aqueous medium wherein N-acetylmannosamine (NAM) is produced by conversion of N-acetylglucosamine to NAM using microorganism having a epimerase enzyme.

Vann(a) et al. teach that NANA synthetase catalyzes the formation of NANA as indicated by its coupling to the CMP-NeuAc synthetase reaction. The reference also teaches that the enzyme condenses Mannosamine and Phosphoenolpyruvic acid (PEP). The reference indicates that it is the first time that anyone has demonstrated an aldolase-independent sialic acid synthetase activity in *E.coli*.

Vann(b) et al. teach the purification, properties and genetic location of above enzyme in *E.coli* K1.

Maru et al. teach a simple and large-scale production of NANA from N-acetylglucosamine (NAG) and pyruvic acid using glucosamine 2-epimerase and N-acetylneuraminate lyase (also called as aldolase), both of which enzymes were isolated and cloned into *E.coli* cells. The reference also teaches the synthesis of NANA from N-acetyl-D-mannosamine (NAM) and pyruvate using aldolase. However, because of the high costs involved in the method wherein the NAM is used the reference suggests the conversion of low cost NAG using the 2-epimerase enzyme to NAM which can be performed in the same reaction vessel.

Thus from the reference of Maru et al. it appears that the manufacture of the sialic acid starting from NAM or NAG and pyruvate using aldolase enzyme was well known in the art. It also appears that it was well recognized in the art that the use of NAM makes the process very

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expensive and methods were developed in the art to cut such costs by using low cost NAG and converting it to NAM using 2-epimerase.

With all the above information found in the prior art and also due to the great commercial demand for sialic acid it would have been obvious to one of ordinary skill in the art at the time this invention was made to bring together all the above information and host cells expressing the above enzymes or culture matter of host cells expressing the above enzymes and simply to put them together and isolate the sialic acid formed. It is well established in the prior art that pyruvic acid and Phosphoenol pyruvic acid are produced literally in every microorganism that undergoes TCA cycle and respiration. Therefore, introducing *E.coli* cells of *Corynebacterium* cell ---as a source of pyruvic acid---, which are well adapted for large-scale culture methods would also be obvious to one of ordinary skill in the art. As opposed to the use of aldolase, with the teachings of Vann (a) and Vann(b) in hand it would also be obvious to one of ordinary skill in the art to replace the aldolase enzyme used in the method of Maru et al. with synthetase enzyme and arrive at the same method of making sialic acid. One of ordinary skill in the art would be motivated to do so because of the great commercial value of sialic acid in food and pharmaceutical industry and to make the same at lower production costs. Due to the important industrial application one would be motivated to develop a method for manufacture of large amounts of sialic acid. One of ordinary skill in the art would have a reasonable expectation of success as Maru et al. demonstrate a small and a large-scale method of making sialic acid using the very same enzymes as in the instant invention and Vann et al. teach an alternate method by way of using synthetase enzyme in place of aldolase and provide the cDNA clone for the same.

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Therefore, the claims 1-3, 6-18 would have been *prima-facie* obvious to one of ordinary skill in the art.

In response to the previous Office action, applicants have traversed the above rejection arguing that none of the references address the claimed features of the present invention. Applicants also argue that Vann et al. teaching of synthetase is not relevant as CMP-NeuAc is not the subject matter of the invention. Examiner respectfully disagrees. Examiner has now rewritten the rejection using the reference of Maru et al. to make the rejection more clear. First of all, contrary to applicants argument, it is well established in the art that sialic acid can be made starting from NAG and converting it to NAM (as using NAM directly make the process more expensive) and using the NAM in the presence of pyruvate and the enzyme aldolase or synthetase. It is also well established that the reaction with aldolase is reversible and can be directed towards making of sialic acid by increasing and maintaining a high concentration of either NAM or pyruvate. With such information having been established it would be obvious to any one of ordinary skill in the art to provide these enzymes in the most productive or low cost manner in the form of recombinant microorganisms comprising the DNA encoding the aldolase/synthetase/epimerase. It is also well known in the art that pyruvate is synthesized literally by every microorganism that is aerobic and respire. Applicants also argue that the reference of Staesche et al. provides an enzyme that is not related to the process of the claimed invention. While the Examiner disagrees with such an argument, in order to make the rejection more clear, Examiner has now used the reference of Maru et al. to maintain the same rejection.

For all the reasons above, the above rejection is *prima facie* obvious to one of ordinary skill in the art and hence the rejection is maintained.

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Conclusion

Claims 4-5 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

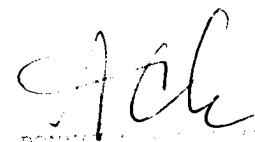
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is

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(703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


MANJUNATH N. RAO, Ph.D.
DIRECTOR, ARTS AND DESIGN
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Manjunath N. Rao. Ph.D.

June 21, 2002